Congenital Hearing Loss

A resident asks...

Why would a primary care physician want to know about the genetics of hearing loss?

Key Points:

- Newborn screening for hearing loss is being implemented in many states.
- Genetic causes are an important contributor to congenital hearing loss and may have implications for risk to future children.
- Discussions with families about genetic testing need to be sensitive to varying cultural attitudes toward deafness.

Learning Objectives for the Congenital Hearing Loss Module

Participants will be able to:

- Understand how newborn hearing screening leads to consideration of genetic etiologies
- Identify common genetic causes of congenital hearing loss
- Recognize cultural differences regarding deafness in the deaf and medical communities

CASE #1

The resident is seeing a newborn, Scott, and his parents, Laura and Jim W. Scott's sister, a 3 year old, has received well child care in your office since she was born. The W's tell the resident that Scott was referred for further evaluation of his hearing - "after he failed his hearing test," the father adds with some sarcasm. They want to know what the test was, and "who ordered it in the first place?" They also want to know what will happen as a result of the referral.

Questions for Discussion:

1. Why is routine newborn hearing screening done?
2. What factors put a newborn at high risk for hearing loss?
3. What type of testing is done?
4. What are the controversies associated with newborn hearing screening?
5. What is the role of informed consent in the screening process?
6. What is the usual follow-up after a newborn screening test indicates hearing loss?

CASE #1 – Discussion

1. Why is routine newborn hearing screening done?

Routine newborn screening is done to detect hearing loss in early infancy, in order to ensure appropriate interventions for language development. Moderate to profound hearing loss in early infancy has been shown to be associated with impaired language development as auditory stimuli during this period is critical to development of speech and language skills. If newborn hearing loss detected on screening is confirmed by definitive diagnosis, then both general therapy and specific treatment based on the etiology of the hearing loss (conductive, sensorineural, or mixed) can be instituted.

Hearing is considered normal if an individual's thresholds are within 15 decibels (dB) of normal thresholds. Hearing loss is categorized by the time period of speech development at which it occurred (prelingual or postlingual); the portion of the hearing system affected (conductive, sensorineural, or mixed) and the degree of loss. Hearing loss is graded as mild (26-40 dB), moderate (41-55 dB), moderately severe (56-70 dB), severe (71-90dB), and profound (90dB). Moderate to profound hearing loss is estimated to occur in approximately 1 out of every 2000 newborns.

For all types of hearing loss, early interventions with speech and hearing therapy are considered key components. The most common type of hearing loss found in neonates is sensorineural. Treatment for this depends on the severity of the loss. Amplification through hearing aids is used in the majority of cases; cochlear implantation is a possibility for profoundly deaf children. Nonrandomized, prospective studies have demonstrated superior communication performance in children with prelingually deafness who received cochlear implants as compared to similar children using more traditional tactile or acoustic hearing aids. Language development can also be fostered in profoundly deaf children through American Sign Language (ASL).

2. What factors put a newborn at high risk for hearing loss?

Neonates are at a higher risk for sensorineural hearing impairment if they have one of the following factors: family history of hearing impairment, congenital or central nervous system infections, ototoxic drug exposure, prematurity, congenital malformations of the head and neck, trauma, and other factors that have led to an admission to an intensive care nursery.

3. What are the controversies associated with newborn hearing screening?

Currently, approximately 35 % of newborns are being screened for hearing loss before hospital discharge according to HRSA reports. The **American Academy of Pediatrics (AAP)** has defined a minimum of five criteria that must be met to justify universal screening. They are:

1. An easy-to-use test that possesses a high degree of sensitivity and specificity to minimize referral for additional assessment is available.
2. The condition being screened for is otherwise not detectable by clinical parameters.
3. Interventions are available to correct the conditions detected by screening.
4. Early screening, detection, and intervention result in improved outcome.
5. The screening program is documented to be in an acceptable cost-effective range

Believing these criteria to be met, the AAP now recommends universal newborn hearing screening. Screening is also recommended by the **American Academy of Audiology**, and **Directors of Speech and Hearing Programs** in State health and welfare agencies, consistent with a 1993 **National Institutes of Health** consensus conference recommending that all infants be screened before hospital discharge. The **Canadian Task Force on the Periodic Health Examination** recommends regular assessment of hearing during well-baby visits during the first 2 years of life using parental questioning and the clap test. However, the **US Preventive Services Task Force** (USPSTF) concludes that there is "insufficient evidence to recommend for or against routine

screening of asymptotic neonates for hearing impairment using evoked oto-acoustic emission (EOE) testing or auditory brainstem response (ABR)." The American Academy of Family Physicians (AAFP) and the USPSTF recommend screening high-risk infants for hearing impairment. The latter two groups are in a process of reviewing their recommendations for scheduled updates.

Arguments made against testing include: 1) the high false positive rate of testing in the face of the low prevalence of disease; 2) the undocumented efficacy of the interventions and 3) concerns by members of the deaf community on the ethics of considering deafness a disability.

Accuracy of screening tests

When you are testing *all* newborns for a disease with a relatively low incidence, even an accurate test can result in a high false positive rate (the percentage of newborns diagnosed with hearing loss when they do not have it.) The type of testing done, as well as background noise in the newborn nursery, and operator skill, also affect the testing results. Because the testing, while often mandated by the state, is performed by individual hospitals, current results vary. Well run, established programs can achieve a false positive rate as low as 3%. New programs, those with insufficient training or tracking of results, or those with significant staff turnover can have false positive rates as high as 20%.

Effectiveness of intervention

The US Preventive Services Task Force notes that, "while the benefits of various treatments for hearing loss seem manifest, no controlled clinical trials have evaluated the effect of early screening on long-term functional and quality-of-life outcomes. Rather, studies of treatment efficacy are generally observational and retrospective, consisting of clinical series or case-control studies of highly selected patients, often with heterogeneous causes of hearing loss, and incompletely defined treatment regimens or protocols of uncertain compliance." They also note that there has been insufficient study of factors that may influence testing such as patient characteristics (e.g., race or ethnic

group, socioeconomic status, level and laterality of hearing loss, the presence of co-morbidity, or developmental delay), family characteristics, and the presence and nature of other therapeutic interventions.

Additionally, there may not be provisions such as financial support to guarantee access to the suggested interventions for all newborns identified with hearing loss; the interventions can only be effective if they can be implemented. Historically, this parallels the early experience with neonatal phenylketonuria (PKU) screening programs. PKU is an inherited condition affecting one in 12,000 newborns. Those affected lack the ability to metabolize phenylalanine; accumulation of phenylalanine in the tissues of the brain results in severe mental retardation. A special diet, including a formula providing phenylalanine-restricted protein, must be maintained at least through adolescence and possibly life long to prevent mental retardation. When the screening process was begun in the 1960's, some newborns identified with this condition remained untreated due to a lack of programs for financial support for those unable to afford the special diet.

Deaf culture

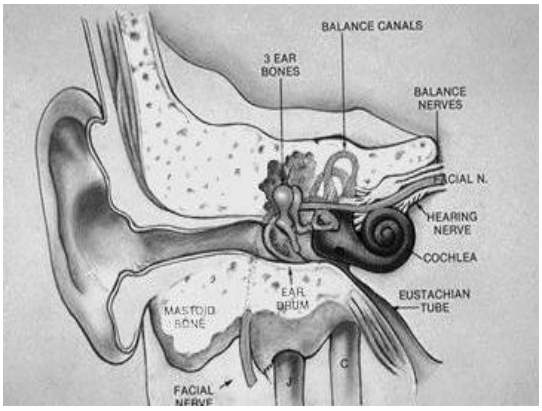
Many members of the deaf community suggest there is an inherent and unwarranted bias in the medical profession that views deafness as a disability or as needing medical intervention. Rather, they view the deaf community as a separate and valued culture in which members are bilingual (communicating in both ASL and English). While this perspective may be more common in parents who are deaf, the view is held in some cases by hearing parents as well. The decision about how to proceed with the evaluation and potential "treatment" of deafness is a personal family matter for the 90% of deaf children who are born to hearing parents as well as those born to deaf parents.

4. What type of testing is done?

Because of their age and development, newborns need a testing method that does not rely on their participation. Currently, auditory brainstem response (ABR) and evoked otoacoustic emissions (EOAE) are used, either alone or in combination. Auditory

brainstem response testing (ABR) measures the electroencephalographic waves generated in response to clicks via three electrodes pasted to the infant's scalp. ABR screening requires the infant to be in a quiet state, but it is not affected by middle or external ear debris. Sensitivity rates have been reported to be 97-100% and specificity rates to be 86-96% in comparison with behavioral testing measures. Despite being the most accurate method, ABR (or modified ABR) is generally not used for a universal *screening* test because of the need for costly equipment and trained operators in all settings.

Evoked otoacoustic emission (EOE) measures sound waves generated by normal cochlear hair cells and detectable with a microphone in the external auditory canal. Using a cutoff of 30 dB to designate hearing impairment, EOE testing has an overall agreement rate with ABR of 91%, with a sensitivity of 84% and specificity of 92%. EOAE may be affected by debris or fluid in the external and middle ear, resulting in referral rates of 5% to 20% when screening is performed during the first 24 hours after birth.



Under the best circumstances, referral rates <4% are generally seen with EOAE combined with automated ABR in a two-step screening system or with automated ABR alone. In a two-step system using EOAE as the first step, referral rates of 5% to 20% for repeat screening with ABR or EOAE may be expected. The second screening may be performed before discharge or on an outpatient basis within 1 month of age. It is recommended by many groups that the screening should be conducted before discharge from the hospital whenever possible.

5. What is the role of informed consent in the screening process?

The **Institute of Medicine Committee Report on Assessing Genetic Risks** defines informed consent as: "a process of education and the opportunity to have questions answered – not merely the signing of a form. The patient should be given information about the risks, benefits, efficacy, and alternatives to testing; information about the severity, potential variability, and treatability of the disorder bring tested for; information

about the subsequent decisions that will be likely if the test is positive; and information about any potential conflicts of interest of the person or institution offering the testing." A formalized informed consent process is used routinely in medicine for procedures, surgical interventions, immunizations, experimental medical regimens such as high-risk chemotherapy, etc. Routine medical care often employs an embedded or implied consent process with differing degrees of shared decision making. An informed consent process is not generally used for other well-established newborn screening programs such as neonatal screening for PKU. The appropriateness of adopting this approach to newborn hearing screening, where there are cultural objections to its implication, needs further thought and discussion. **Table 1** lists different state newborn hearing screening programs and the role of parental informed consent in those programs.

Table 1: Newborn Hearing Screening Legislation in the United States

States	Year passed	Full implementation by:	Requires screening of:	Advisory committee established	Covered benefit of health insurance	Report to state DOH	Provision of educational materials?	Informed consent by parents?	Liability immunity?	Religious objection exclusion?
Arkansas	1999	July 1, 2000	Hospitals >50 births	Yes	Medicaid	Yes	Yes			Yes
California	1998	Dec. 31, 2002	Acute care hospitals with CCS funding	Yes	Medicaid	Yes	Yes	Yes	Yes	Yes
Colorado	1997	July 1, 1999	85% of newborns	Yes		Yes	Yes			
Connecticut	1999	July 1, 2001	All babies			Yes	Yes			Yes
Georgia	1999	July 1, 2001	95% of newborns	Yes		Yes				
Hawaii	1990	N/A	All babies							
Illinois	1999	Dec 31, 2002	All babies	Yes		Yes	Yes			Yes
Indiana	1999	July 1, 2000	All babies	Yes	Yes					Yes
Kansas	1999	Not Specified	All babies			Yes	Yes	Yes		Yes
Louisiana	1999	July 1, 2000*	All babies	Yes						
Maryland	1999	July 1, 2000	All babies	Yes	Yes					
Mass.	1998	Not Specified	All babies	Yes	Yes		Yes			Yes
Mississippi	1997	Jan. 1, 1998	All babies	Yes					Yes	
Missouri	1999	Jan. 1, 2002	All babies	Yes	Yes	Yes	Yes			Yes
New York	1999	April 1, 2000	All babies		Yes	Yes				
North Carolina	1999	Not Specified	All babies			Yes				
Oregon	1999	July 1, 2000	Hospitals >200 births	Yes		Yes	Yes			Yes
Rhode Island	1992	N/A	All babies	Yes	Yes					Yes
Texas	1999	April 1, 2001	Hospitals >100 births		Yes	Yes	Yes	Yes	Yes	
Utah	1998	July 1, 1999	All babies	Yes		Yes		Yes		
Virginia	1998	July 1, 2000	All babies	Yes		Yes	Yes			Yes
West Virginia	1998	July 1, 2000	All babies	Yes	Yes	Yes	Yes			Yes
Wisconsin	1999	July 1, 2003	88% newborns							
Wyoming	1999	July 1, 1999	All Babies					Yes		

6. What the usual follow-up after a newborn screening test indicates hearing loss?

Upon referral, the neonate undergoes evaluation by a multidisciplinary team experienced in the evaluation of neonatal deafness. Hearing loss is categorized by the portion of the hearing system affected (conductive, sensorineural, or mixed); whether it is primarily due to a genetic cause or environmental one (hereditary or acquired), and if genetic, whether or not it is a component of a genetic syndrome (syndromic or non-syndromic).

The incidence of congenital hereditary hearing impairment is 1:2000 neonates. Of these neonates, 70% have non-syndromic hearing loss. 75-80% of cases of non-syndromic hearing loss are due to autosomal recessive genetic conditions, and of these, 50% are due to DFNB1 mutations. DFNB1 related hearing loss has approximate prevalence in the general population of 14/100,000 (~1/7,000).

Other causes of congenital severe-to-profound hearing loss that should be considered in children who represent isolated (or sporadic) cases in their family are CMV (cytomegalovirus, the most common cause of congenital, non-hereditary hearing loss), prematurity, low birth weight, low APGAR scores, infection, and any illness requiring care in a neonatal intensive care unit.

Physical examination focuses on findings associated with syndromic forms of hearing loss, including the presence of retinitis pigmentosa (Usher syndrome), thyroid enlargement (Pendred syndrome), cardiac conduction defects (Jervell and Lange-Nielsen syndrome), and pigmentary abnormalities (Waardenburg syndrome). (See **Tables 2 and 3**).

Table 2
Selected syndromes inherited in an autosomal recessive manner (in decreasing frequency)

Syndrome	Frequency	Hearing loss	Associated findings	Gene(s) involved	Genetic testing available
Usher	most common AR	sensorineural	retinitis pigmentosa		research only
Pendred	2nd most common	Abnl bony labyrinth	Euthyroid goiter at puberty; vestibular sx	*PDS* gene (chrom locus 7q22-q31)	clinical
Jervell and Lange-Nielsen	3rd most common		syncopal episodes and sudden death (prolonged QTc)		high risk families
Refsum disease	rare	sensorineural	retinitis pigmentosa; faulty phytanic acid metabolism		clinical

Table 3
Selected syndromes inherited in an autosomal dominant manner (in decreasing frequency)

Syndrome	Frequency	Hearing loss	Associated findings	Gene(s) involved	Genetic testing available
Waardenburg	most common AD	sensorineural	pigmentary abnormalities; +/- limb abnml., Hirshsprung	*PAX3*, *MITF*, *EDNRB*, *EDN3*, *SOX10*	clinical
Branchiootorenal	2nd most common	conductive, sensorineural, or mixed	branchial cleft cysts or fistulae, malformations of the external ear including preauricular pits, and renal anomalies.	*EYA1* gene in 30%	clinical
Stickler		sensorineural	cleft palate, and spondyloepiphyseal dysplasia resulting in osteoarthritis	STL1, STL2, and STL3.	clinical
Neurofibromatosis II	rare	2nd to bilateral vestibular schwannomas	flat dysplastic tumors or subcutaneous spherical nodules of the peripheral nerves on the limbs and trunk at risk for a variety of other tumors including meningiomas, astrocytomas, ependymomas, and meningioangiomatosis	NF2	clinical

CASE #2

Return visit of CASE #1, 7 months later

Scott was diagnosed with a hearing loss associated with a DNFB1 mutation. He has been doing well with speech and hearing therapy. The family is considering cochlear implants for him. They want to discuss with you what they have learned from the subspecialists they have seen and have questions about whether or not they should get prenatal testing with their next pregnancy.

Questions for Discussion:

1. What is DNFB1 (connexin 26) related hearing loss?
2. What is the role of genetic testing?

CASE #2 – Discussion

1. What is DNFB1 (connexin 26) related hearing loss?

DFNB1 related hearing loss is characterized by congenital (present at birth), non-progressive sensorineural hearing impairment. Usually, the hearing impairment is severe or severe-to-profound; however it can range from mild to severe in different families and within a family. Except for the hearing impairment, affected individuals are healthy and enjoy a normal life span. Vestibular function is normal; affected infants and young children do not experience balance problems and learn to sit and walk at age-appropriate times.

DFNB1 related hearing loss is suspected in patients who have (1) congenital, non-progressive sensorineural hearing impairment that is mild-to-profound by auditory brainstem response testing (ABR) or pure tone audiometry; (2) no related systemic findings identified by medical history or physical examination. They may also have a family history consistent with autosomal recessive inheritance of hearing loss (for example, an affected sibling). However, the majority of people with autosomal recessive diseases represent the first known case in their family. The diagnosis of DFNB1 related hearing loss is confirmed if the patient has recognized disease-causing mutations in the gene *GJB2* (chromosome 13q11-12) that alters the connexin 26 (Cx26) protein. DNA-based testing of the *GJB2* gene detects about 95% of disease-causing mutations. The most common mutation, 35delG, is found in over two-thirds of persons with DFNB1. About 30% of patients with DFNB1 have other identifiable disease-causing mutations in *GJB2*; at least 21 other disease-causing mutations have been identified. Available methods of screening for Cx26 mutations have failed to identify disease-causing mutations in some families in whom the diagnosis of DFNB1 has been established by linkage studies; thus, failure to detect a Cx26 mutation does not exclude the diagnosis of DFNB1 (see **GeneClinics** summary for further information).

2. What are the reasons for doing genetic testing?

It is important to ascertain and address the questions and concerns of the family/individual when considering genetic testing. Families often want to know the cause of their child's hearing loss. Finding out that it is a genetic cause can often prove comforting, both because of the certainty of a diagnosis is preferred over uncertainty and because it may relieve guilt - "Was it something I (we) did during the pregnancy that caused this?" Conversely, some individuals feel more guilt knowing that the child's condition was inherited from them. The diagnosis of a DNFB1 mutation implies that the child will have a normal life span. It does not differentiate how this child would fare with a cochlear implant as compared to individuals with other sensorineural causes of profound hearing loss.

In addition, a genetic diagnosis may have implications for reproductive decision-making. Prenatal testing is available for couples at 25% risk of having a child with DFNB1 and in whom the disease-causing mutations are known. DNA extracted from cells obtained from amniocentesis at 16-18 weeks' gestation or chorionic villus sampling (CVS) at 9-11 weeks' gestation can be analyzed. In this way, the genetic potential for hearing loss can be diagnosed in utero. Parents may also wish to consider the risk for a child with hearing loss in deciding whether or not to have more children. Genetic counseling, a process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions, can assist families in determining the role of genetic testing or knowledge of genetic risk in their lives.

Carrier detection may be relevant in the reproductive counseling of other relatives of an affected individual. DNA-based testing can only be considered if a disease-causing mutation has been identified in an affected family member. Subsequently, the relatives at risk to be gene carriers can be tested using the same laboratory techniques.

Many deaf individuals are interested in obtaining information about the underlying etiology of their hearing loss rather than information about reproductive risks as they do not consider themselves to be handicapped but define themselves as part of a distinct culture with its own language, customs, and beliefs. Genetic testing may thus sometimes serve as an explanation for etiology rather than as a factor in reproductive decision-making.

Follow-up: After genetic counseling, and reflection over time by the W. family, they decided not to get prenatal counseling with their next child because "they couldn't imagine deciding not to have another child like Scott." The perceived burden of hearing loss may differ widely across families. The role of the provider in counseling about prenatal genetic testing is to assure that the families understand the legitimacy of their choices.

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